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14. ABSTRACT
Spinal cord injury (SCI) is frequently accompanied by traumatic brain injury (TBI), but evidence-based approaches for treatment of this "dual-diagnosis" are lacking. This project proposed using current clinical-practice evidence to guide development of an animal model to provide a new tool for studying the biological mechanisms involved, and to open new directions for therapeutics for combined injury. We initially established an animal model of dual injury that reflected an unexpected complexity of interactions between these injuries. The group then focused on building a clinical TBI+SCI patient database from San Francisco General Hospital, the Santa Clara Valley Medical Center and from the VA Palo Alto Health Care System, that detailed the acute and chronic stages of recovery after dual-injury. This required development of common data elements and methods for querying different types of patient records. We now have an overview of recovery and the medications given to the SCI+TBI patients. Interestingly, more medications are used in the dual-diagnosis patients than for each injury alone, resulting in altered recovery. These clinical data were used to guide hypothesis development for testing agents in the newly established model of SCI+TBI. The first agent tested, topiramate, confirmed our suspicion that drug effects differ with injury type, improving one and retarding the other. The project has resulted in a continuing community of practice and research and the animal model should continue to inform and be informed by the clinical enterprise

15. SUBJECT TERMS
spinal cord injury, traumatic brain injury, dual diagnosis

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Translational Research Partnership

SCI with Brain Injury: Bedside-to-Bench Modeling for Developing Treatment and Rehabilitation Strategies

Progress Report
09/30/2010- 09/29/2013

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INTRODUCTION

The goal of this Translational Research Partnership was to gather information on clinical outcomes and practices from several collaborating neurotrauma programs and synthesize this information to inform the development of relevant animal models of the dual diagnosis of Spinal Cord Injury (SCI) and Traumatic Brain Injury (TBI). These models are being used to identify improved therapeutic strategies that can be tested in the clinical setting. The process is meant to be iterative and interactive, producing a "community of practice and research."

The project links the Brain and Spinal Injury Center at the University of California, San Francisco (UCSF) with the Spinal Cord Injury and Brain Injury units at the Santa Clara Valley Medical Center (SCVMC) and the VA Palo Alto Health Care System (VAPAHCS).

During the project, a teleconferencing system was established to facilitate communication among the study sites, and all Investigators participated in a series of meetings which rotated between participating medical centers to develop clinical database search strategies and information dissemination during the project. The search strategies allowed us to synthesize a dual diagnosis database, which is reported in more detail below.

A dual injury model in rats was developed and initial drug testing was accomplished. It was learned that dual injuries produce complicated outcomes depending on the site of injury and that treatments that improve recovery after spinal cord injury do not necessarily promote recovery after brain injury.

BODY

In the text below, we have taken the Statement of Work as a template and detailed how each aim was completed and milestones accomplished.

Specific Aim 1: Develop community of practice and research and

focus groups; and develop clinical database search strategy and dual diagnosis data

Task 1: Continue development of community of practice and research and focus groups

1a. All Investigators' meetings

The Principal and Partnering Investigators have continued to meet to develop the community of practice and research linking the basic scientists working on animal models of brain and spinal cord injury with the clinical scientists working with patients having spinal cord injuries and traumatic brain injuries. During the second year of the project, this community has continued to develop and has grown to include several new members. Face-to-face meetings have been held at the VAPAHCS and UCSF as described below.

1b. Teleconference set up

Telephone and internet-based audio conferencing has been set up to facilitate collaboration and reduce the amount of time spent in traveling between institutions in different parts of the Bay Area. WebEx software has been used to allow multicast audio.

1c. Teleconferences

Telephone conferences have been held twice a month on average (see KEY RESEARCH ACCOMPLISHMENTS).

Milestones:

Focus Groups (FG) have continued to be conducted at major national and international conferences.

- Combined conference of International Spinal Cord Society and American Spinal Injuries Association, Washington, DC, 2011

Meeting of Drs. Beattie, Creasey and McKenna with Dr. Fin Biering-Sorensen, President of International Spinal Cord Society, regarding Common Data Elements which he has championed internationally. Focus group with hand therapists from Cleveland Ohio and VA Palo Alto. Participation in symposium on Common Data Elements.

- American Spinal Injuries Association, Denver, Colorado 2012

Meeting of Drs. Beattie, McKenna and Creasey with Dr. Sukvinder Kalsi-Ryan who developed the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) for assessment of hand function, and Lisa Johansen, PhD, RPT, who is using it at VAPAHCS.

- International Spinal Cord Society, London, England, 2012

- Stanford Symposium on Regeneration, Repair and Restoration of Function after Spinal Cord Injury, November 16-17 2012.
- VAPAHCS SCI+TBI Research Forum meetings – March 16, 2012, and March 15, 2013. Presentations by partnering PI, Graham Creasey (2012) and poster presentations describing consensus reports (Inoue et al., 2012 and Guandique et al., 2013) were also made.

Task 2: Develop clinical database search strategy

Developing a clinical database search strategy was accomplished in year one of the grant. Access to the databases and review of the charts continued during year two and into year 3. The information desired was difficult to obtain and it was necessary to establish and a number of approaches were used. Individual chart review, text mining software for content analysis, attempts to run principal component analysis, were all used to evaluate the records. The data available covered different time spans post-injury, so comparing details across the three sites was difficult. Reviews of individual patient charts to identify medications used at the time of initiation of rehabilitation and at the time of discharge from acute rehabilitation were done. These trends in medication use and discontinuation were provided to the animal model group in an effort to model clinical practice from the bedside to bench.

Task 3: Query Dual Diagnosis clinical database

The investigators obtained data from the SCI and the TBI Systems of Care at SCVMC, San Francisco General Hospital, and the SCI Service and the Polytrauma Center at VAPAHCS.

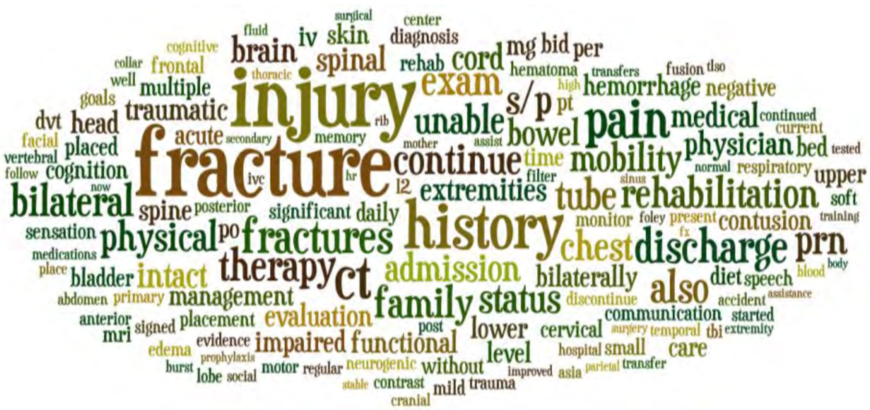
3a1. SCI and TBI Systems of Care at SCVMC

Patients who had undergone TBI rehabilitation at SCVMC between 1989 and 2010 were identified in the TBI Model Systems (TBIMS) National Database when the Form I (enrollment data) also indicated the presence of an SCI.

The admission and discharge notes of patients (n=14) with combined TBI and SCI diagnosis were then extracted from the hospital records of SCVMC and text mined in detail. The text was parsed into a database that was designed to track the treatment and recovery of the patients throughout the time spent in the brain and spinal rehabilitation facility. Once the database was compiled, an initial comparison utilizing a word cloud analysis of admission and

discharge notes was used to provide the first broad visualization of the database.
In this word cloud analysis, the larger a word is in size, the more frequently it appears in the document. In the example below, “fracture” appeared in high frequency. We determined that many of the TBI and SCI patients had undergone multiple fractures at the time of their injury. This was in keeping the expectation that TBI and SCI patients experience multiple co-morbidities or “polytrauma.”

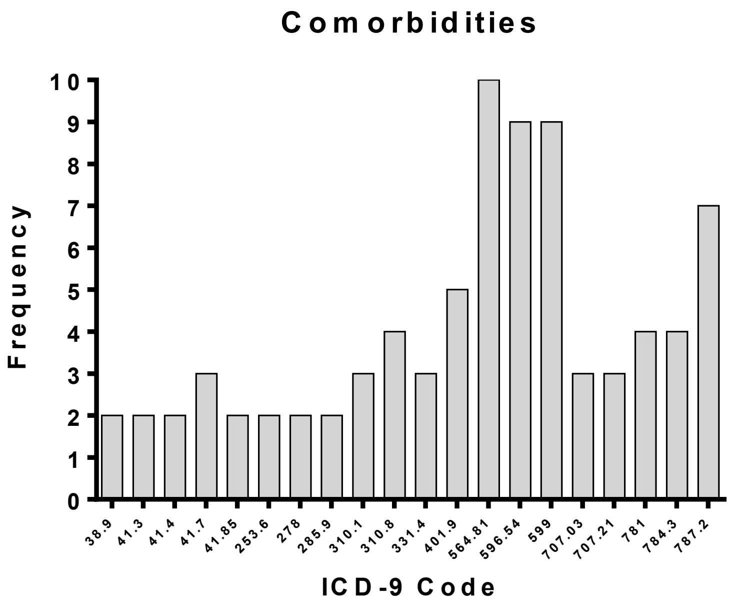
Admission notes:



Discharge notes:

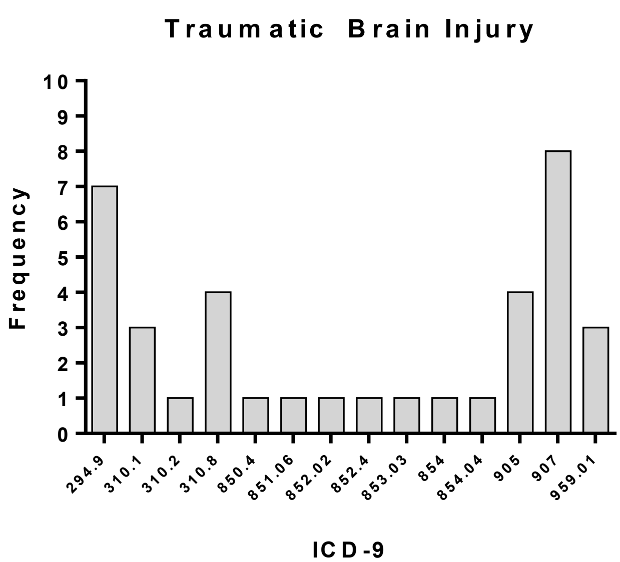
The patient cohort with SCI+TBI had a total of 343 unique International Classification of Diseases, Ninth Edition (ICD-9) codes, confirming the variety of comorbidities in this sample. A histogram of

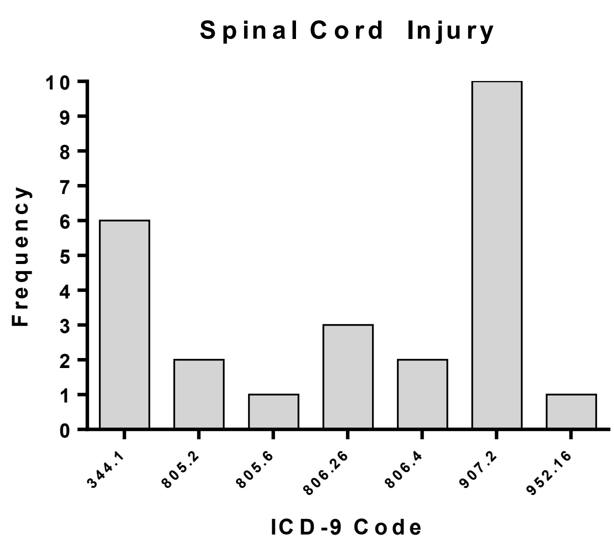
the twenty commonest ICD-9 codes for co-morbidities is shown below.



Type	Code	Subject(s)
SEPTICEMIA NOS	38.9	1, 8
K. PNEUMONIAE INFECT	41.3	13, 14
E. COLI INFECTION	41.4	1, 14
PSEUDOMONAS INFECT NOS	41.7	8, 9, 12
GRAM-NEG BACT INFECT NEC	41.85	4, 13
NEUROHYPOPH DISORD NEC	253.6	4, 8
OBESITY NOS	278	4, 9
ANEMIA NOS	285.9	3, 12
PERSONALITY CHANGE CCE	310.1	1, 7, 14
OTH NPMD FOLLOWING OBD	310.8	1,2, 8, 10
OBSTR HYDROCEPHALUS	331.4	1, 4, 8
HYPERTENSION NOS	401.9	1, 4, 8, 11, 13
NEUROGENIC BOWEL	564.81	1, 4, 7, 8, 9, 10, 11, 12, 13, 14
NEUROGENIC BLADDER NOS	596.54	1, 4, 7, 8, 9, 11, 12, 13, 14
URINARY TRACT INF NOS	599	1, 4, 7, 8, 9, 10, 12, 13, 14
PRESSURE ULCER-LOW BACK	707.03	4, 9, 14
STAGE I PRESSURE ULCER	707.21	8, 12, 14
ABN INVOL MOVEMENT NEC	781	3, 8, 12, 14
APHASIA	784.3	8, 11, 12, 13
DYSPHAGIA	787.2	1, 4, 8, 9, 11, 12, 13

ICD-9 codes commonly associated with TBI and SCI respectively were extracted from the hospital records and are shown in the two charts below.





Type	Code	Subject(s)
PERSIST MENT DIS CCE NOS	294.9	1, 3, 4, 6, 8, 12, 13
PERSONALITY CHANGE CCE	310.1	1, 7, 14
POSTCONCUSSION SYNDROME	310.2	1
OTH NPMD FOLLOWING OBD	310.8	1, 2, 8, 10
CONCUSSION-DEEP COMA	850.4	6
CORTEX CONTUSION-NEC	851.06	2
TRAUMATIC SAH-BRIEF	852.02	1
TRAUMATIC EXDH-NOS	852.4	8
OTH TRAUM ICH-MOD	853.03	11
OTH INTRACRANIAL INJURY-NOS	854	4
OTH INTRACRANIAL INJURY-LONG	854.04	6
LATE EFF SKULL/FACE FX	905	8, 11, 12, 13
LATE EFF IC INJURY	907	1, 2, 3, 4, 6, 8, 10, 14
HEAD INJURY NOS	959.01	1, 7, 10

Type	Code	Subject(s)
PARAPLEGIA	344.1	7, 9, 10, 12, 13, 14
FX DORSAL VERTEBRA-CLOSE	805.2	9, 13
FX SACRUM/COCCYX-CLOSED	805.6	1
T7-T12 FX-CL/COMP CRD	806.26	4, 9, 14
CL LUMBAR FX W CORD INJ	806.4	6, 10
LATE EFF SPINAL CORD INJ	907.2	1, 2, 3, 4, 7, 9, 10, 12, 13, 14
T7-T12 COMPL CORD LESION	952.16	7

Patients were coded with a variety of ICD-9 codes, and individual patients were often coded with more than one ICD-9 code for their SCI and also for their TBI. Note that only 13 out of 14 patients had an ICD-9 code that referenced a traumatic brain injury, and only 11 out of 14 patients had an ICD-9 code that referenced a spinal cord injury.

This indicates that using ICD-9 codes to search hospital records for patients with TBI, SCI, and both TBI and SCI is not a sufficient search strategy to identify all such patients. The search strategy actually used to identify these patients identified individuals who would have not have been found merely by searching for appropriate ICD-9 codes.

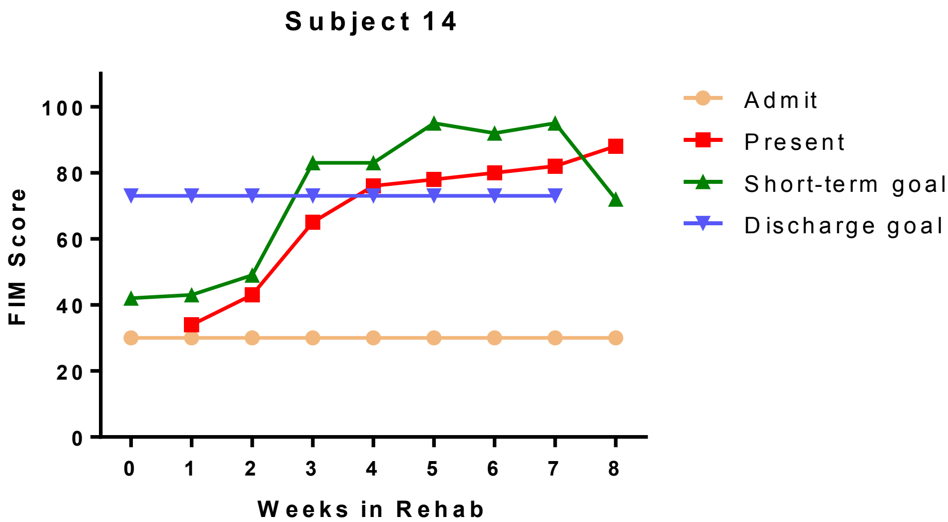
We extracted demographic data of the TBI and SCI patients in the database to provide a targeted analysis that would provide essential information for further hypothesis testing. The analysis below includes age, gender, etiology of injury, number of days until admission into rehab, length of stay in rehabilitation, and Glasgow Coma Scale (GCS). In addition, the database includes data on injury specifics, surgical procedures, diagnostic findings, physical and neurological exam findings, and rehabilitation assessment plans.

Demo-graphic	**Age**		**Gender**		**Etiology**		**# days until rehab admission**		**Rehab LOS**	
Data	Mean years	SD	% Male	% Female	%Vehicular	% Fall	Mean days	SD	Mean days	SD
TBI/SCI (N =14)	33.6	17.1	71	28.6	78.6	21.4	29.6	24.4	55.9	39.7

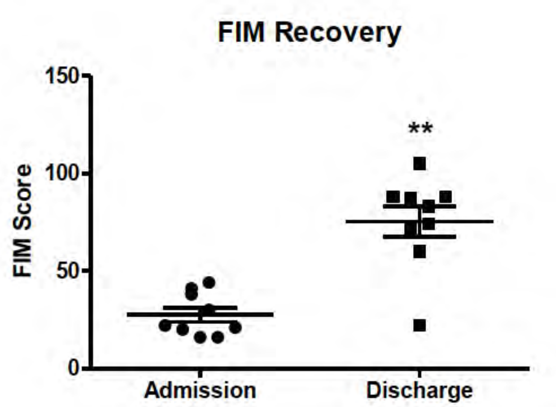
Glasgow Coma Scale	**Mild (13-15)**	**Moderate (9-12)**	**Severe (<= 8)**	**Not Reported**
TBI/SCI (N = 14)	14.29%	7.1%	64.3%	14.3%

In addition, we obtained de-identified Functional Independence Measure (FIM) scores that tracked the functional recovery of the TBI

and SCI patients during their stay in rehabilitation. FIM graphs were plotted against the number of weeks spent in rehabilitation. We were able to visualize the functional recovery of each patient throughout rehabilitation. For example, the analysis below shows a single patient with a dual TBI and SCI.



TBI/SCI Patients Improve in Functional Independence During Length of Stay in Rehabilitation.



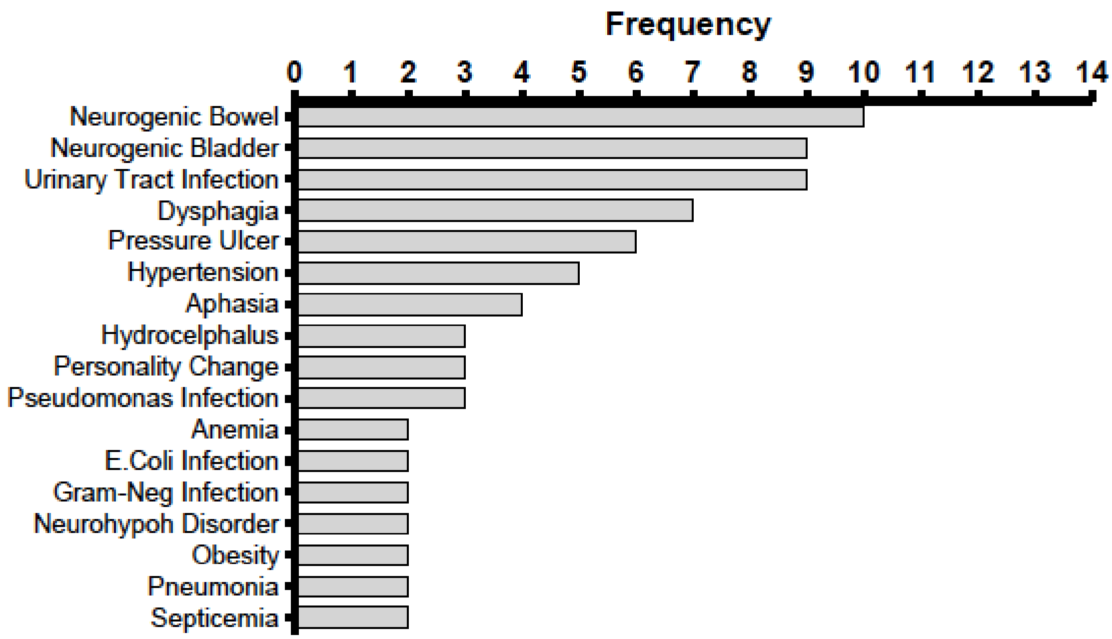
In addition to the various measures included in the database, the majority of the patients (n=9) were also assessed for functional independence at the time of admission and discharge using the FIM All of the patients assessed on the FIM showed low total FIM scores at the time of admission into the rehab facility (27.6 ± 11.0). By the time patients were discharged from rehab (43.1 ± 30.1 days), all but 1 patient had substantial recovery in their FIM scores (75.4 ± 23.7). Unfortunately we did not have any data regarding injury severity for either TBI or SCI for this patient to assess what was contributing to this lack of functional recovery. Despite this outlier, there was an overall significant increase in FIM between admission and discharge in this patient group (p = 0.0017). We also observed a non-significant relationship regarding the correlation of FIM scores and length of stay

in rehab. There is a stronger negative correlation for FIM scores at the time of discharge and their total length of stay at the rehab facility ($R^2 = 0.62$), compared to their FIM scores at the time of admission and how long they stayed in rehab ($R^2 = 0.29$). Regarding the relationship of injury severity to FIM scores, there is a significant difference between ASIA A and ASIA D severities of SCI both at the time of admission and discharge ($p = .047$), and both groups show equally significant recovery in FIM over time ($p < .0001$). However, GCS severities for SCI do not show a significant trend to FIM scores, for either admission ($R^2 = 0.13$) or discharge ($R^2 = 0.003$).

SCI but not TBI severity significantly impacts length of stay in rehab. SCI and TBI severities were assessed with the ASIA and GCS measures, respectively, in comparison to length of stay in rehab to determine which type of injury is a stronger contributor to the time it takes for patients to be discharged. We found a significant increase in the length of stay for ASIA A subjects (71.7 ± 9.3 days) compared to ASIA D subjects (29.0 ±12.2 days, $p = 0.02$), however there was not a significant difference in length of stay between the different GCS severities either as groups ($p = 0.52$;, or as a correlation of GCS scores to length of stay ($R^2 = 0.05$). This is not explained by a higher incidence of severe TBI and SCI occurring together, since there was no significant difference in GCS scores between ASIA A and ASIA D groups ($p = .32$), and there does not appear to be a significant correlation between the neurological level of SCI and TBI severity ($R^2 = 0.26$). However, there is a large difference in the distribution of age at time of injury for males versus females. Even though most of the subjects in this cohort were males (71%), as a group they sustained their injuries over many age ranges (39 ± 17 years), whereas females only sustained their injuries at a very young age (19 ± 1.7 years).

<u>The incidence of comorbid conditions in TBI/SCI patients was assessed.</u> ICD-9 codes referenced in the medical records were mined and categorized for their respective conditions (see figure below) . Each condition was quantified for how many patients were diagnosed. The most prominent comorbid condition in these patients was neurogenic bowel (n=10) and bladder (n=9). This was also accompanied by a large number of patients also diagnosed with urinary tract infections (UTI) (n=9), consistent with autonomic dysfunction commonly seen in SCI patients [26, 27]. About half of the

patients also developed complications with swallowing (n=7), pressures sores (n=6), and hypertension (n=5), with additional complications associated with infections and neurological complications.



Medications suggest increased depression and infections, decreased pain, and continual constipation during length of stay. Medications referenced in the medical records were quantified for each patient at the time of admission and discharge to determine how many patients were being treated for various comorbid conditions, and how that changed during their length of stay. Most of the patients were treated for constipation at the time of admission (n=10), consistent with the number of comorbid cases of neurogenic bowel (see figure above), and all but 1 patient continued to suffer from this condition by the time of discharge. Almost half of the patients were being treated for depression by the time of discharge (n=6), and even fewer patients being treated for acid reflux, pain, and muscle spasms. Fortunately, most of the patients being treated for pain at the time of admission (n=8) no longer needed to take pain medication at discharge (n=1), and a few patients also no longer needed to be treated for other ailments, including anxiety, ulcers, infections, and other complications that presented at the time of admission.

Word frequency analysis of medical records highlight important information during recovery. We leveraged the admission and discharge notes to determine if additional useful information regarding these patients could be harnessed from word frequency analysis see figure below. There were more total words mined from the admission notes (19,552) than the discharge notes (12,484), and each word cloud is a representation of the percentage each word represents compared to the total words for each group. The four most relevant and frequent words seen in both the admission and discharge word clouds were fracture (1.26% and 1.23%), injury (0.95% and 0.91%), rehabilitation (0.58% and 0.74%) and pain (0.50% and 0.68%), respectively. We also assessed the relative

change these top occurring words were being mentioned between admission and discharge to highlight important changes in the state of the patients that may not be obvious from other aspects of the database. The percentages for each discharge word were subtracted

from the percentage for the same admission word and a new word frequency cloud was generated from the changes, and color coded to reflect increases (green) and decreases (red). Of these top four words, the mention of rehabilitation (+0.167%) and pain (+0.180%) both increased by the time of discharge. Additional words that increased in frequency that were noticed were the mention of improve (+0.118%), treatment (+0.115%), neurogenic (+0.101%) and hematoma (+0.118%). The most notable decreases in frequency over time were unable (-0.236%), cognition (-0.119%), impaired (-0.096%) and therapy (-0.144%). It was also noted that there was an increase in the mention of admission (+0.218%), and a decrease in the mention of discharge (-0.316%), which seems counter-intuitive at first. However, there may have been discussion about plans for discharge when the patient was admitted, and likewise the discharge notes may frequently reference improvements or changes from when they were admitted, and may be disregarded in future analyses.

In summary, we have succeeded in building a clinical TBI and SCI patient database from the Santa Clara Valley Medical Center models system database that details the acute as well as the chronic stage of recovery. We are currently preparing these data for publication (Guandique et al., 2013 in preparation).

3a2. SCI Service and the Polytrauma Center at VAPAHCS

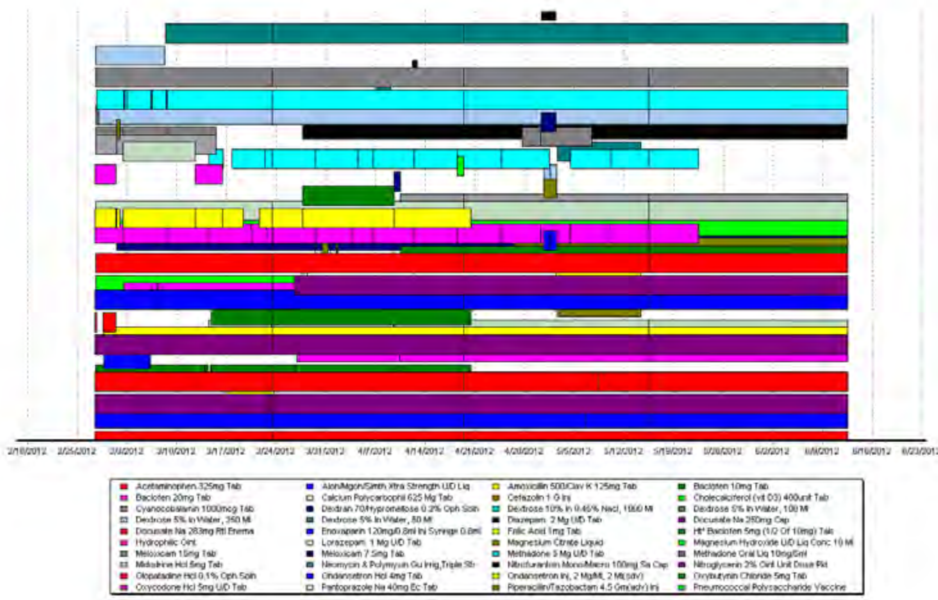
The strategy used with the Santa Clara Valley records was initially used as a model for extracting data on patients with TBI and SCI in the VA Palo Alto Health Care System, but the considerable differences between these two health care systems necessitated different approaches. The Polytrauma Service at VAPAHCS was founded in 2005, unlike the Model TBI System which has been in operation since 1989. As a result, a search of patients admitted for TBI rehabilitation only identified three patients who also had SCI. The records of patients recently admitted to the VA SCI Service for rehabilitation after acute SCI were therefore searched to identify those with TBI. The full text of all notes on these patients were searched for phrases such as “TBI” and “GCS,” and the context of these phrases was examined to determine the way they were used (for example, excluding patients in which the notes recorded that “TBI was ruled out”).

This search strategy showed that of an initial cohort of the 45 patients

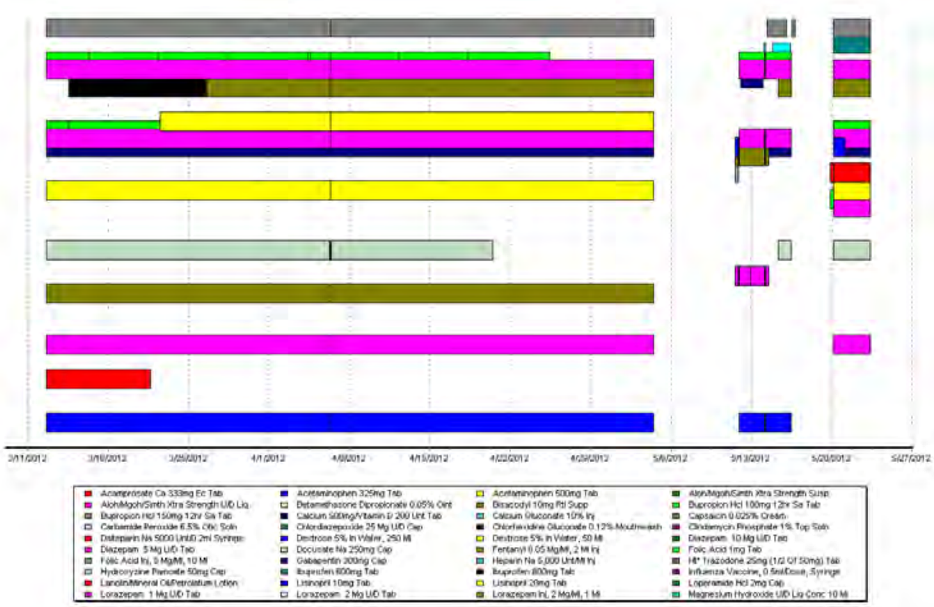
most recently admitted to the SCI Service for rehabilitation after acute SCI, ten (22%) had a TBI. As with SCVMC, we found that ICD-9 codes did not provide a reliable search strategy for identifying SCI and TBI patients.

To provide an initial overview of medications we produced a medication cloud that tracked duration of all medications prescribed during admission for acute rehabilitation. A medication cloud is shown for both a SCI patient and a TBI + SCI patient to provide a brief visualization of medications that were administered and their duration. Note the greater numbers of medications used in the Dual Diagnosis patient.

SCI+TBI patient at VA



SCI only patient at VA



A database of patients with spinal cord injuries or disorders currently served by the Spinal Cord Injury Service of the VA Palo Alto Health Care System was searched for patients who had been admitted for initial rehabilitation or subsequent care during the period October 1st 2010 to October 19th 2012. The electronic medical records of these patients in the VA Computerized Patient Record System were then searched for any reference to traumatic brain injury. The search strategy included examining the list of Active Problems and searching the text of all Notes electronically for any of the following text phrases: "TBI", "brain injury", "brain trauma", "head injury", "head trauma", "loss of consciousness", "LOC", "CVA" or "cognitive". When any of these words or phrases were found, their context was examined to determine whether the patient did indeed have a history of traumatic brain injury and its relationship in time to the spinal cord injury. Every note from the SCI Psychologists includes a section on cognitive functioning that was identified by this search; each of these notes was then read to determine whether there was cognitive impairment and whether it was attributable to the TBI or to other conditions. Other information was also extracted, such as age, gender, cause of SCI damage, and level and completeness of the spinal cord lesion.

701 patients with spinal cord injury or disorder were identified as having been admitted to the SCI Service either for initial rehabilitation or subsequent care, during a period of just over two years between October 1st 2010 and October 19th 2012. Of these, 675 were male and 26 were female, as is typical in the veteran population with SCI. 409 were identified as having sustained traumatic SCI and 292 as having non-traumatic SCI.

Traumatic and Non-traumatic SCI by Gender

SCI	**Male**	**Female**	**Total**	**Mean Age**	**Range**
Traumatic	400	9	409	60 $\pm$ 13	23 ÷ 93
Non-Traumatic	275	17	292	64 $\pm$ 13	24 ÷ 96
Total	**675**	**26**	**701**	**62 $\pm$ 13**	**23 ÷ 96**

Non-traumatic SCI by etiology

Etiology of SCI	Male	Female	Total
Arthritic	42		42
Infection or abscess	22	2	24
Herniated disc	6		6
Motor neuron disease (ALS)	32	1	33
MS	70	10	80
Multifocal motor neuropathy	1		1
Muscular Dystrophy	1		1
Myelopathy	28	1	29
Poliomyelitis	4		4
Syringomyelia	3		3
Tumor	26		26
Vascular change	22	1	23
Other non-traumatic	15	2	17
Unknown	3		3
Total	**275**	**17**	**292**

Of the 409 patients with traumatic SCI, 99, or 24.3%, had a TBI at the same time as the SCI and a further 17 had a TBI on a different occasion to the SCI. The level and completeness of the SCI in the 99 patients with a concurrent TBI is shown in the Table below.

Level and completeness of SCI in patients with concurrent TBI

	Tetraplegia	Paraplegia	Total
Complete	9	22	31
Incomplete	47	21	68
Total	**56**	**43**	**99**

Of the 99 patients with concurrent SCI and TBI, only 18 had TBI noted in their Active Problem list. The other patients were identified by electronically searching the text of notes. Most commonly, the TBI was mentioned in the text of notes by psychologists working in the SCI Service, and sometimes when reviewing a patient years after the injury, but not in the history recorded on admission.

The numbers of patients with concurrent SCI and TBI who were recorded as having cognitive impairment related to their TBI are shown in the Table below, sorted by etiology of SCI according to the

Common Data Elements classification. The most frequent cognitive impairments were short-term memory loss and slowed processing speed.

<u>Cognitive impairments in vets with SCI+TBI by etiology of SCI</u>

Etiology of SCI	**SCI with TBI**	**Cognitive Impairment**	**%**
Sports	12	6	50.0
Assault	2	1	50.0
Transport	58	30	51.7
Fall	24	17	70.8
Other traumatic	3	0	0.0
Total	**99**	**54**	**54.5**

The table below shows the etiology of SCI in all patients with traumatic SCI and in those with concurrent SCI and TBI. When the SCI was due to assault, concurrent TBI was rare. Of 47 cases of SCI due to assault, 39 were due to gunshot wounds and none of these 39 had concurrent TBI. The two cases with concurrent SCI and TBI due to assault were caused by shrapnel and a rocket propelled grenade respectively. If cases of assault are excluded, 97 out of 362 patients with SCI, or 26.8%, had suffered a concurrent TBI.

<u>Traumatic SCI and TBI by etiology (females in parentheses)</u>

Etiology	**Total**	**SCI with TBI**	**%**	**unrelated brain injury**
Sports	56	12	21.4	1
Assault	47	2	4.2	3
Transport	219 (7)	58 (3)	26.5	8
Fall	73 (1)	24 (1)	32.9	2
Other trauma	14 (1)	3 (1)	21.4	3
Total	**409 (9)**	**99 (5)**	**24.2**	**17**
Total (not including Assault)*	***362 (9)****	***97 (5)****	***26.8****	***14****

The table below shows when the concurrent injuries occurred in relation to military service. While 30 of the cases of SCI and TBI occurred during active military duty, the majority of these occurred during transport by road or air.

Concurrent SCI and TBI by relation to active military duty

Etiology of SCI	**During active duty**	**After leaving military**	**Total**
Sports	2	10	12
Assault	2	0	2
Transport	20	38	58
Fall	5	19	24
Other traumatic	1	2	3
Total	**30**	**69**	**99**

When patients are stratified according to the date of their traumatic SCI, it is notable that records of concurrent TBI have increased greatly over the last four decades. Since 2001 the prevalence of concurrent TBI in these patients with traumatic SCI has been recorded as 39.4%, and when patients whose SCI was caused by gunshot wound or shrapnel [assault?] are excluded, this figure rises to 42.7%. Possible reasons for this are discussed below.

Concurrent SCI and TBI by etiology and date of injury

	2012-2001			**2000-1991**			**1990-1981**			**1980-1952**		
Etiology of SCI	SCI	SCI + TBI	%	SCI	SCI + TBI	%	SCI	SCI + TBI	%	SCI	SCI + TBI	%
1.Sports	17	8	47.1	4	1	25.0	16	1	6.3	19	2	10.5
2.Assault	13	1	8.0	8	0	0	3	0	0	23	1	4.3
3.Transport	55	27	49.1	38	17	44.7	37	4	10.8	89	10	7.5
4.Fall	47	18	38.3	12	2	16.7	6	2	33.3	8	2	25.0
5.Other traumatic	5	0	0	2	0	25.0	2	1	50	5	2	20.0
Total	137	54	**39.4**	64	20	**31.3**	64	8	**12.5**	144	17	**11.8**
Total not including Assault	124	53	**42.7**	56	20	**35.7**	61	8	**13.1**	121	16	**13.2**

The prevalence of concurrent TBI in SCI patients in this retrospective study when averaged over six decades (24.2%) is similar to figures from the SCI Model Systems reported in 1995 (28.2%), but lower than figures from a prospective study in a single SCI Model System reported in 2008 (60%). SCI Model Systems tend to admit younger patients with a higher proportion of women, sometimes sooner after injury, However, the prevalence recorded in this study has increased significantly over this period.

There are several possible reasons for the increase in numbers of veterans with traumatic SCI recorded in this study as having a concurrent TBI, from less that 12% before 1980 to at least 40% since 2001.

a. military activity

In recent years, traumatic head injury has been described as the signature injury of military action in the Middle East, and it might be hypothesized that this has increased the number of SCI patients with TBI. However, patients whose SCI was caused by gunshot wound or shrapnel showed a much lower prevalence of TBI in this study, presumably because the missile struck either the spine or head but rarely both, and in recent conflicts the use of body armor appears to have greatly reduced the incidence of spinal cord injuries. It is well known that during active military duty many injuries are caused not in combat but by other forms of trauma such as motor vehicle accidents. In this study, while 30% of concurrent injuries occurred during active military duty, the majority of these occurred during transport by road or air. Only one was due to shrapnel and one was due to a rocket propelled grenade and none were due to gunshot. Only seven of 99 concurrent injuries occurred during combat: two occurred in motor vehicle accidents, three in flying accidents, only one was due to shrapnel and none to gunshot. It seems likely therefore that the contribution of military combat to increasing records of concurrent SCI and TBI is small.

b. improved documentation

The computerized Patient Record System was introduced in 1995. Patients injured before this time have their current medical records entered into this system but the records of their medical history before this time are heavily dependent on their memory, which can be impaired by head injury, and on being asked about the possibility of past head injury.

c. improved awareness

Awareness of head injury in military personnel has increased during the last two decades, and this has led to increased screening in the Department of Defense and in the Department of Veterans Affairs. Psychologists working in SCI units are usually aware of this, but other staff, including medical residents in training who may do much of the documentation, may be less aware of the possibility of head injury and less skilled in diagnosing it.

Traumatic SCI usually has obvious symptoms and signs and is

therefore relatively rarely missed, and major TBI is rarely missed. When both are present, management is usually assigned to either a SCI Unit or a TBI Unit, depending on the relative severity of the two injuries. Ideally the staff of such units would collaborate in the management of such patients. In practice, SCI Units and TBI Units may not be located in the same institution, and even when they are, they often have different cultures and collaboration may be limited. In practice each unit will concentrate on the injury it knows best, and the other injury may not receive state-of-the art attention.

Less severe TBI can be missed, particularly in patients with multiple and life-threatening injuries who may be in shock, undergoing emergency surgery, sedated, or on a ventilator. When they are stabilized, their management will depend somewhat on the service to which they are transferred, and on its awareness of the possibility of concurrent injuries.

Identification of TBI in records of patients with SCI in this study was inconsistent. It might be thought that this was because the head injury was mild in this series of patients, but Table 4 shows that over 50% of the veterans with concurrent TBI and SCI were identified as having cognitive impairment. This is similar to the percentage found in SCI patients treated in the Model SCI Systems of Care. While cognitive impairment can be due to causes other than TBI in these patients, it remains important to identify whether they have had a TBI.

In the case of patients with mild TBI, it might have been argued in the past that they did not suffer greatly from delayed or absent documentation of it, but there is now increased interest in the unknown long term effects of mild and repeated TBI on conditions such as Parkinson's disease and dementia. The fact that the VA follows patients with SCI for life offers an opportunity to study the relationship between these conditions.

The use of an electronic medical record in the VA has had many advantages, but it may be necessary to structure the collection and recording of some information in a more consistent way that could be implemented in a national system of care. Screening of SCI patients for TBI during their initial rehabilitation would help to avoid missing the diagnosis of TBI. If TBI resolves there is no way to identify it subsequently other than history from the patient, collaterals and prior medical reports. Screening will need to be done after patients are stabilized on medications for pain and spasticity since they are known to affect cognitive functioning until patients accommodate to them.

Patients will also need to be clear of delirium from surgical anesthesia, UTIs and other SCI complications. In many cases it will be impossible to distinguish TBI from depression, PTSD and/or anxiety, so diagnosis will be delayed until psychiatric symptoms are adequately treated. These are some of many reasons for providing adequate time for rehabilitation rather than discharging patients as soon as they can survive. Fortunately adequate admission time is standard practice in VA.

The PrOMOTE research project currently being carried out in the VA to study the effect of a more comprehensive approach to vocational rehabilitation is using detailed interviews of veterans in which they are asked about any prior history of head trauma. Of the first 100 SCI patients in the VA Palo Alto SCI Service to undergo these interviews, 70% reported having had a head injury, although not necessarily concurrently with their SCI. (Elspas - personal communication). It is possible therefore that the prevalence of 40-45% reported in this paper is still an underestimate, so there may still be a significant number of veterans in whom TBI has not been diagnosed.

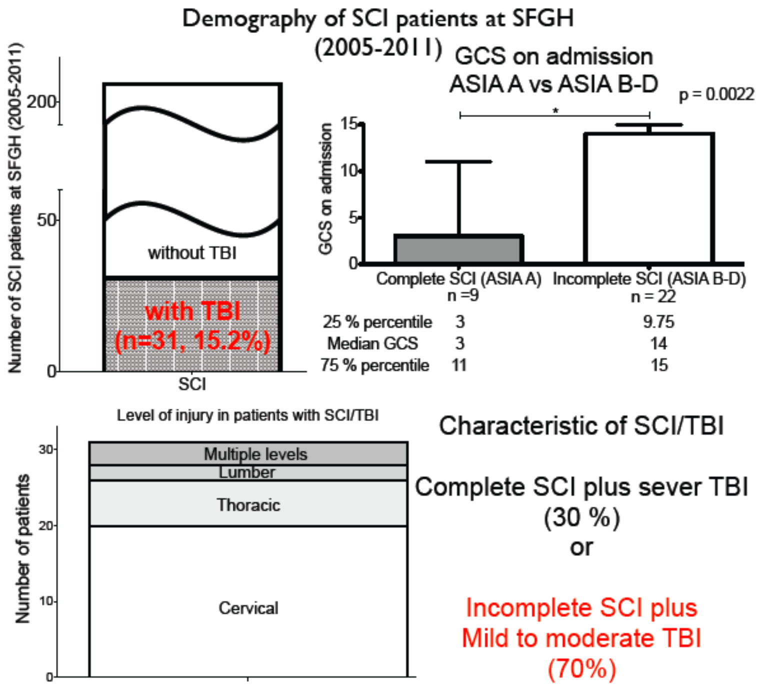
The causes of SCI in veterans with concurrent TBI resemble the causes seen in the civilian population. It would be of interest to determine comparable figures for the civilian population, particularly as electronic medical records are being adopted. This could best be done within the SCI Model Systems, even though only a minority of US civilians with SCI receive their care in this system and it may have a higher proportion of patients with severe spinal cord injuries than in the population treated outside the SCI Model Systems.

Conclusions

1. Documentation of TBI in this population of veterans with traumatic SCI was inconsistent: in patients with both SCI and TBI, the TBI identified by searching the Notes was only recorded among the Active Problems list in the electronic medical record 18% of the time, and was often absent from admission histories and discharge summaries.
2. Records of TBI in veterans with traumatic SCI in this study have increased from less than 12% before 1980 to over 40% since 2001. This may reflect improved documentation and increased awareness, but there may be further cases that are still not being identified. Extrapolation of these figures nationally suggests that there may be a substantial number of veterans whose TBI has not been documented.
3. Improved screening and documentation would help to identify all

SCI veterans with TBI and allow appropriate management and long term follow up.

3a3. Patients at UCSF/SFGH. Under the supervision of Dr. Manley, Dr. Tomoo Inoue examined the demographics and clinical picture for 203 SCI patients admitted to SFGH from 2005-2012. Of these, 31 were charted as having concurrent TBI. The ASIA grades were frequently not noted in the charts, and Dr. Inoue reviewed the available information and assigned a grade. In this data pool, approximately 15% had co-occurring TBI. These data were reported, in part, in an abstract presented at the annual Society for Neuroscience meeting in New Orleans (October, 2012)(Inoue et al, 2012). Patients with complete SCI were more likely to have a lower ASIA score than those with incomplete SCI. The level of injury was predominantly cervical, although a little over a third had thoracic, lumbar or multiple level injuries. Since patients treated at the acute neurotrauma center at SFGH are discharged to rehabilitation centers (including the SCVMC and, rarely, the VAPAHCS, rehabilitation measures are not easily available for this cohort, although we have excellent early data for them. One of the goals is to provide better early care data from the VA and SCVMC cohorts, and better long-term outcome data for the SFGH cohorts.



3b. Comparison of SCVMC, VAPAHCS, and SFGH/UCSF

A patient's rehabilitation outcome is greatly influenced by the amount of time that passes before they are admitted for rehabilitation. We determined the number of days between the date of injury and the date of admission into rehabilitation, and also the length of stay in

rehabilitation, and compared these between SCVMC and the VAPAHCS hospitals. The analysis is shown below:

Days till Admission to Rehabilitation		
Location	Mean	St Dev
VA (N = 10)	51.5	31.3
SCVMC (N = 14)	29.6	24.4

*No statistically significant difference (T-test)

Length of Stay in Rehabilitation		
Location	Mean	St Dev
VA (N = 10)	96.5	51.4
SCVMC (N = 14)	55.9	39.7

*Statistically significant difference (T-test, p <.05)

Note that the length of stay in rehabilitation is shorter in SCVMC, a civilian hospital, than VAPAHCS, a VA hospital.

The medications provided to Dual Diagnosis patients were compared between these two hospitals. The most common medications prescribed for these patients on admission to rehabilitation at each hospital are shown below:

Admission Medications			
VA	Frequency	SCVMC	Frequency
DOCUSATE	9	DOCUSATE	10
ACETAMINOPHEN	9	ACETAMINOPHEN	7
SENNA	9	SENNA	4
BISACODYL	7	BISACODYL	5
OMEPRAZOLE	7	OMEPRAZOLE	1
ALBUTEROL	6	ALBUTEROL	2
LIDOCAINE	5	LIDOCAINE	1
ASCORBIC ACID	4	ASCORBIC ACID	2
HYDROCODONE/ACETAMINOPHEN	4	HYDROCODONE/ACETAMINOPHEN	2
ONDANSETRON	4	ONDASENTRON	1
ENOXAPARIN	3	ENOXAPARIN	3
GABAPENTIN	3	GABAPENTIN	2
DOXYCYCLINE	3	DOXYCYCLINE	1
LISINOPRIL	3	LISINOPRIL	1
CHLORHEXIDINE	2	CHLORHEXIDINE	2
METOPROLOL	2	METOPROLOL	2
DEXTROSE	2	DEXTROSE	1
MICONAZOLE	2	MICONAZOLE	1
HEPARIN	1	HEPARIN	3
FENTANYL	1	FENTANYL	2
BACLOFEN	1	BACLOFEN	1
FERROUS SULFATE	1	FERROUS SULFATE	1
QUETIAPINE	1	QUETIAPINE	1

Note that the most common medications were those prescribed for management of the neurogenic bowel (e.g docusate, senna, bisacodyl), together with mild analgesics, antacids and bronchodilators.

We compared this with the medications prescribed at the time of discharge from rehabilitation. The most common medications prescribed on discharge are shown below:

Discharge Medications			
VA	Frequency	SCVMC	Frequency
ACETAMINOPHEN	10	ACETAMINOPHEN	7
DOCUSATE	8	DOCUSATE	8
OMEPRAZOLE	8	OMEPRAZOLE	1
SENNA	7	SENNA	4
LIDOCAINE	5	LIDOCAINE	1
ONDANSETRON	5	ONDASETRON	1
GABAPENTIN	4	GABAPENTIN	2
ASCORBIC ACID	4	ASCORBIC ACID	1
BISACODYL	4	BISACODYL	1
TRAZODONE	3	TRAZADONE	5
BACLOFEN	3	BACLOFEN	3
OXYCODONE	3	OXYCODONE	2
LACTOBACILLUS	3	LACTOBACILLUS	1
MICONAZOLE	3	MICONAZOLE	1
FERROUS GLUCONATE	2	FERROUS GLUCONATE	1
SIMVASTATIN	2	SIMVASTATIN	1
METOPROLOL	1	METOPROLOL	1

Note that some bowel medications (docusate and senna) are still among the most commonly prescribed, together with mild analgesics and antacids, but albuterol and low molecular weight heparin have been discontinued and the use of baclofen has increased. The most common medications with potential effects on the central nervous system at the time of admission are shown below.

Medications of Interest
HALDOPERIDOL, OLANZAPINE, RISPERDONE
IBUPROFEN, CELCOXIB, ASPRIN
LEVETIRACETAM, VALPROIC ACID
MODAFINIL, AMANTADINE
CITALOPRAM, BUPROPION
METOCLOPRAMIDE, DROPERIDOL
BACLOFEN
GABAPENTIN
LORAZEPAM
METHADONE
EPOETIN ALPHA
METFORMIN
DOCYCLINE

In the third year of the grant, pilot testing with some of these medications in the combined injury animal model will be undertaken. We will assess gabapentin and baclofen as two of our first drug targets. In addition, we plan to expand the clinical database to allow more detailed comparison of the SCVMC database with the VAPAHCS database so that both can be mined for hypotheses and refined through our community of practice and research.

Specific Aim 2: Develop baseline incomplete SCI plus mild-complicated and moderate TBI rat protocols and outcomes
PI: Michael S. Beattie, PhD
Site: UCSF

Task 1: Factorial combination studies on SCI+TBI
An experimental animal model for combined SCI and TBI was developed to help drive mechanistic studies of dual diagnosis. A manuscript describing this model was published in Experimental Neurology (248:136-147, 2013). For these studies, rats received a unilateral SCI (75 kdyn) at C5 vertebral level, a unilateral TBI (2.0 mm depth, 4.0 m/s velocity impact on the forelimb sensori-motor cortex), or both SCI + TBI. TBI was placed either contralateral or ipsilateral to the SCI. Behavioral recovery was examined using a bvariety of outcome measures including paw placement in a cylinder (forebrain guided exploration), grooming, open field locomotion, and the IBB cereal eating test (object manipulation). Over 6 weeks, in the paw placement test, SCI + *contralateral* TBI produced a profound deficit that failed to recover, but SCI + *ipsilateral* TBI dramatically enhanced use of the paw on the SCI side. In the grooming test, SCI + *contralateral* TBI produced worse recovery than either lesion alone even though *contralateral* TBI alone produced no observable deficit. In the IBB forelimb test, SCI + *contralateral* TBI revealed a severe deficit that recovered in 3 weeks. For open field

locomotion, SCI alone or in combination with TBI resulted in an initial deficit that recovered in 2 weeks. Thus, TBI and SCI affected forelimb function differently depending upon the test, reflecting different neural substrates underlying, for example, exploratory paw placement and stereotyped grooming. Concurrent SCI and TBI had radically different effects on outcomes and recovery, depending upon laterality of the two lesions. Recovery of function after cervical SCI was retarded by the addition of a moderate TBI in the contralateral hemisphere, but recovery was markedly enhanced by an ipsilateral TBI. These findings emphasize the complexity of recovery from combined CNS injuries, and the possible role of plasticity and laterality in rehabilitation, and provide a start towards a useful preclinical model for evaluating effective therapies for combine SCI and TBI.

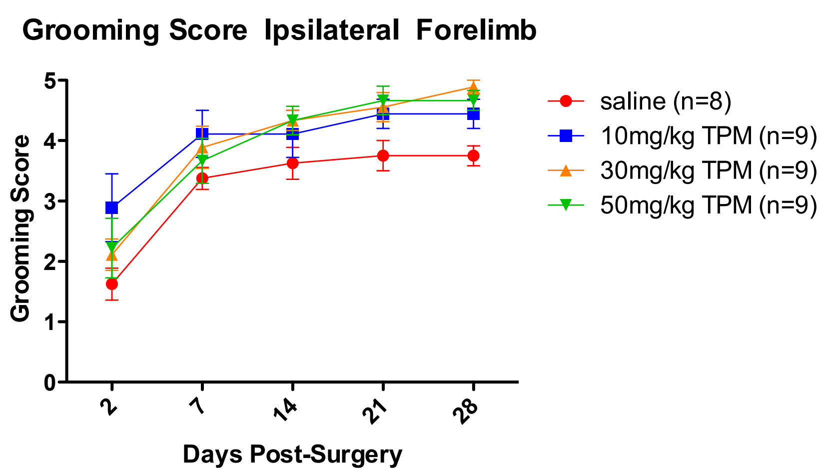
Milestone: This paper (Inoue et al., 2013) is included in the appendix.

Specific Aim 3: Test clinic-driven hypotheses for improving outcomes in the dual diagnosis animal model

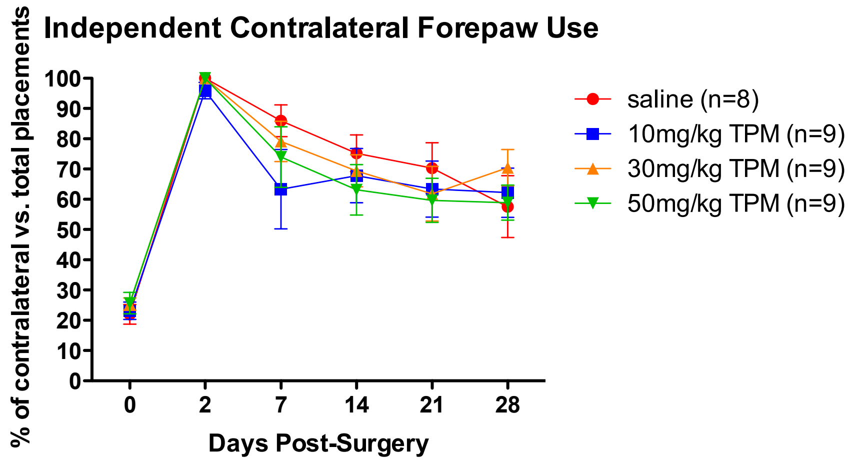
PI: Michael S. Beattie, PhD

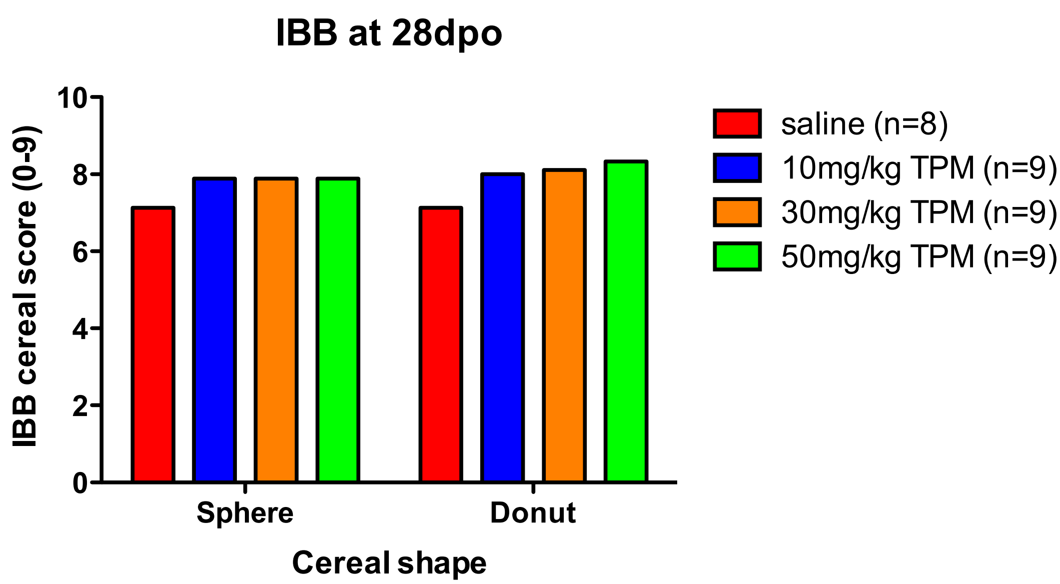
Site: UCSF

Tasks 1-3. Based on the outcomes of the model development studies, we decided to combine Tasks 1-3 by selecting a treatment that has multiple targets. The drug, topiramate, has a variety of properties including anti-epileptic, analgesic and neuroprotective qualities (Angehagen et al, 2003) and is a currently FDA approved agent which makes it potentially available for rapid clinical application. It has been shown to reduce allodynia and hyperalgesia in a pain model of chronic nerve constriction (Benoliel et al, 2006); reduce lesion size in stroke models and reduce consequent behavioral deficits as well (refs). Thus, topriamate seemed a good drug to test for efficacy in both the TBI and SCI contexts. To determine whether this drug has efficacy in a model of SCI, and to identify an effective dose, we first tested topiramate in a dose-response study using the spinal cord injury model alone. We found that topiramate at all doses improved forepaw use for grooming behavior (see graph above), as well as spontaneous forepaw use in the cylinder (see graph below; better performance is a lower score in this schema), and for food



manipulation testing using the IBB cereal eating test (data shown below), all tests that were differentially sensitive in the combined injury model. Topiramate also appeared to reduce tissue damage suggesting that after SCI, it is neuroprotective. (These data will be presented at the Society for Neuroscience Annual Meeting (Nov. 3, 2013; Beattie et al., 2013).



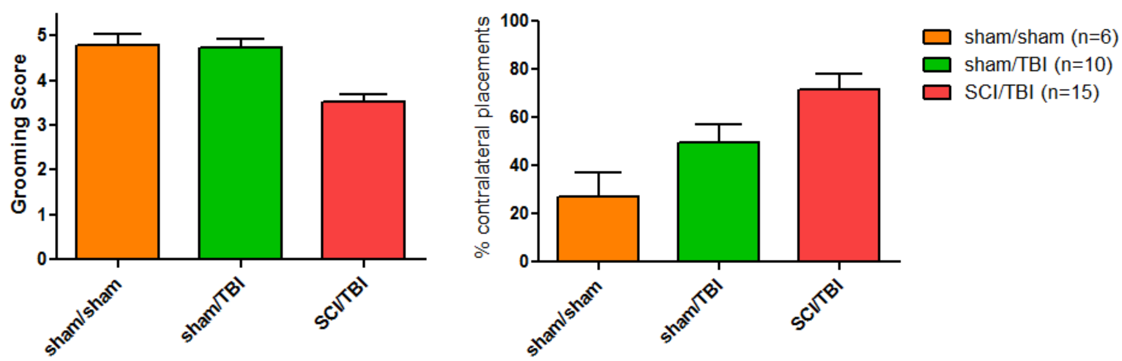


We then chose to examine the 50 mg/kg dosing of topiramate (TPM) in a second phase of the experiment, as this dose is frequently used clinically for seizure control. The following six groups were included:

1) sham SCI, sham TBI, TPM treatment (n=3)
2) sham SCI, sham TBI, Saline (n=3)
3) sham SCI, TBI, TPM treatment (n=5)
4) sham SCI, TBI, Saline (n=5)
5) SCI, TBI contralateral to the SCI, TPM (n=8)
6) SCI, TBI contralateral to the SCI, Saline (n=7)

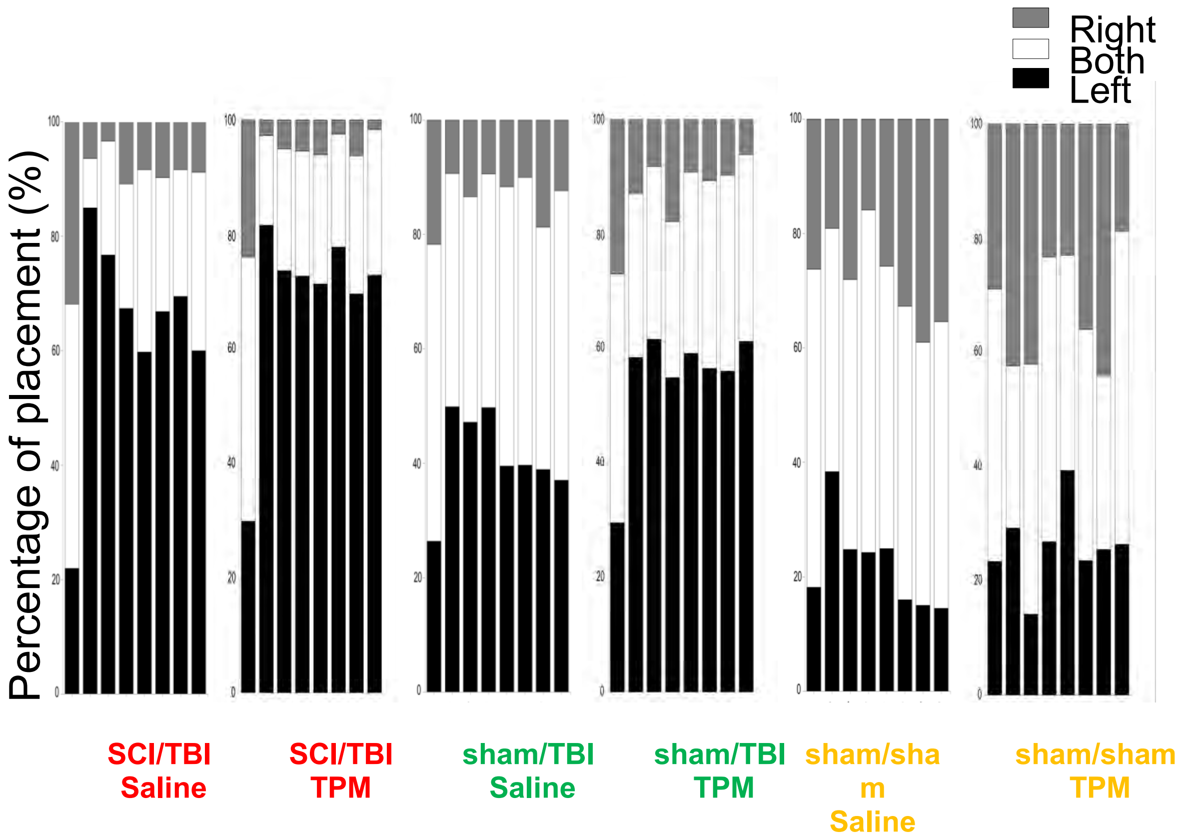
The first two groups are treatment and surgical controls; the second two groups have TBI lesions, one with and one without topiramate a treatment, and the 5th and 6th groups have a combined injury (i.e. both a SCI and TBI contralateral to the SCI), one with and one without topiramate treatment.

First, we replicated the finding from Inoue, et al. (2013) on the primary outcome measures (grooming, paw placement, and cereal eating), showing a differential effect of lesion condition (TBI alone, and SCI+TBI contra) on grooming and paw placement (both main effects $p<0.001$).



The treatment with topiramate, however, did not affect recovery of grooming across groups, but grooming was little affected by TBI. Paw placement showed an interesting and unexpected response to the treatment. The illustration below shows paw use for each paw independently (right or left) and together (both) over the 6 week observation period. The right paw is ipsilateral to the spinal cord injury and contralateral to the TBI. Comparing the sham groups (far right 2 groups), one can see that the right and left paw are used independently about equally and both are used about half the time. Introducing a TBI (middle two groups) causes the right paw (contralateral to the lesion) to be used significantly less and the left paw and both paws more. The topiramate treatment exacerbated this effect. The SCI plus TBI showed the greatest effect on the right paw use and the topiramate worsened this slightly. TPM produced a non-significant (p =.057) trend for worse recovery pooled across the TBI and TBI+SCI

groups on paw placement. The histological analysis for this study is underway. We think that this is a potentially interesting example of what we hypothesized in



the grant--a drug therapy that has a beneficial effect and in SCI, but may impair recovery in SCI+TBI.

This study is being prepared for publication (Morioka et al., 2013).

Specific Aim 4: Combine information from clinical practice queries and animal model results to plan for dual diagnosis guidelines
PIs: G. Creasey, MD, S. McKenna, MD, G. Manley, MD, PhD, M. Beattie, PhD
Site: VAPA, SCVMC and UCSF
Tasks 1 - 3. Begin to gain consensus on needed changes in current practice, begin the process for establishing new guidelines for dual diagnosis treatment and continue community input into hypotheses to be tested in the animal model. The community of practice and research has been established, and while this last specific aim may have been somewhat over-ambitious for this 3 year award,

the group continues to meet for this purpose. We will continue to interact for the next three years under the support of the DoD on an another award that has similar goals of matching animal models with clinical reality.

KEY RESEARCH ACCOMPLISHMENTS. (See detailed report above.)

REPORTABLE OUTCOMES

Meetings and Papers

National Neurotrauma Society Annual Meeting, Fort Lauderdale, Fl 2011 Combined traumatic brain injury and cervical spinal cord injury in the rat: Additive and dissociated effects on neurological outcomes. Tomoo Inoue, Amity Lin, Xiao Kui Ma, Jinghua Yao, Xiaoming Yao, Yvette Nout, Stephen McKenna, Graham Creasey, Geoffrey T. Manley, Adam R. Ferguson, Jacqueline C. Bresnahan, Michael S. Beattie.

Santa Clara Valley Brain Injury Conference, February 24-26, 2011.
"Dual Diagnosis with Brain and Spinal Cord Injury: An Interactive Assessment."

VAPAHCS TBI Research Forum, March 16, 2012
"Combined traumatic brain injury and cervical spinal cord injury in the rat: additive and dissociated effects on neurological outcomes."
Inoue T, Lin A, Ma X, Nout Y, McKenna S, Creasey G, Manley G, Ferguson R, Bresnahan J, Beattie M.

International Spinal Cord Society Meeting, London, England July 2012. Effects of combined unilateral cervical spinal cord injury (SCI) and traumatic brain injury (TBI) in the rat. J.C. Bresnahan, T. Inoue, G. Creasey, S. McKenna, A. Ferguson, G. Manley, M. Beattie

Society for Neuroscience Annual Meeting, New Orleans LA, October 12-17, 2012. "Combined brain and spinal cord injury: Clinical picture and an animal model." Inoue T, Lin A, Ferguson A, Creasey G, McKenna S, Manley G, Bresnahan J, Beattie M.

VAPAHCS TBI Research Forum, March 15, 2013
Development of a database for combined brain and spinal cord injury. Guandique, C.F.[1], Nielson, J.L.[1], Arellano, C.A.[1], Kosarchuk, J.J.[2], Doan, R.[2], Inoue, T.[1], Wright, J.[2], Manley, G.T.[1], McKenna, S.L.[2], Creasey, G.H.[3], Bresnahan, J.C.[1], Beattie, M.S.[1], Ferguson, A.R.[1].

Society for Neuroscience Annual Meeting, Nov 2013. Big –data visualization for translational neurotrauma. Neilson JL, Inoue T, Paquette J, Lin A, Sacramento J, Liu AW Guandique CF, Irine KA, Gensel JC, Manley GT, Carlsson GE, Lum PY, Beattie MS, Bresnahan JC, Ferguson AR.

Society for Neuroscience Annual Meeting, Nov 2013. The AMPA receptor antagonist topiramate improves recovery of function following unilateral cervical contusion injury. Beattie, M.S., Lin, A., Huie, J.R., Ferguson, A.R., Bresnahan, J.C.

Inoue T, Lin A, Ma X, McKenna S, Creasey GH, Manley GT, Ferguson AR, Bresnahan JC, Beattie MS. Combined SCI and TBI: Recovery of forelimb function after unilateral cervical spinal cord injury (SCI) is retarded by contralateral traumatic brain injury (TBI), and ipsilateral TBI balances the effects of SCI on paw placement. Exp Neurol, 2013; 248:136-147.

Manuscripts in Preparation

Guandique CF, Nielson JL, Kosarchuk JJ, Wright j, Doan R, Inoue T, Liu AW, Ferguson AR, Manley GT, Bresnahan JC, Creasey GH, Beattie MS, McKenna SL (2013) Development of a Translational Database for Combined Traumatic Brain Injury and Spinal Cord Injury. Manuscript in preparation.

Creasey GH, et al. (2013) Prevalence of traumatic brain injury among US veterans with spinal cord injury. Manuscript in preparation.

CONCLUSION

This project has accomplished the majority of its tasks for this Translational Research Partnership. We have developed a community of practice and research for SCI and TBI in the San Francisco Bay Area of California and conducted focus groups to determine needs and attitudes of clinicians and others to these diagnoses and the potential for modeling the combined diagnosis in animals. We have queried several databases representing veterans and civilians with TBI and SCI and conducted a preliminary merge of clinical databases available for these diagnoses and developed a search strategy for determining the scope of the problem and the areas of priority for animal modeling. On this basis, a rodent model of combined SCI + TBI has been designed and created by the Principal Investigators at the Brain and Spinal Injury Center at UCSF, and has been used to compare the outcomes of SCI, TBI and combined SCI and TBI in this animal model. We have tested a treatment in this model and have found interesting interactions between the SCI and combined SCI+TBI models. An ongoing collaboration has been established between the

Principal and Partnering Investigators to interpret the data being obtained, and to define improved outcome measures and treatment practice information based on both the new animal model of combined injury and the merged databases.